scope of the claims. The amendment to claim 1 makes express a step that was inherent in the method and does not alter the scope of the claim.

**Drawings.**

Applicants note the Examiner's acknowledgement that the application has been filed with informal drawings and that formal drawings will be required when the application is allowed.

**35 U.S.C. §112, First Paragraph:**

Claims 11, 52, 55, 56, were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reason ably convey to one skilled in the art that the inventor's at the time the application as filed had possession of the invention, Applicants respectfully traverse.

**Claim 11:**

The Examiner alleged the limitation "wherein step (ii) is performed at about 4°C", claimed in claim 11, has no clear support in the specification and claims as originally filed. Applicants traverse.

Claim 11, as amended herein recites:

> The method of claim 1, wherein step (ii) comprises a wash performed at about 4°C.

At page 48, lines 16-18, the specification states:

> After 2 hours of incubation at 37°C, the wells were quickly washed 6 times with **ice cold PBS** and 3 times for 10 minutes each with 4 mL of stripping buffer (50 mM glycine pH 2.8, 0.5 M NaCl, 2M urea, 2% polyvinylpyrrolidone) at RT. [emphasis added]

One of skill in the art would readily recognize that "ice cold PBS" is at a temperature of about 4°C. Accordingly the specification demonstratges that Applicants were in possession of amethod that involved washing the target cells with a wash that is about 4°C. Accordingly the rejection of claim 11 under 35 U.S.C. §112, first paragraph, should be withdrawn.

**Claim 52:**

The Examiner alleged the limitation in claim 52 "live cells of a subtractive cell line" has no clear support in the specification as originally filed. Applicants traverse.

At page 25, lines, 21-23, the specification teaches that:

> [I]n a preferred embodiment the target cell (grown adherent to a tissue culture plate) is co-incubated with the subtracting cell line (in suspension) in a single cell culture flask.

The specification clearly teaches the coincubation of a live subtractive cell line with the target cells.

In addition, the specification states that:

> **Virtually any cell** can act as a subtractive cell. However, in a preferred embodiment, **subtractive cells display all the markers on the target cell except the marker (*e.g.* receptor) that is to act as a target for** selection of the desired binding antibodies or binding polypeptides. Particularly preferred cells are thus closely related to the target cell(s), in terms of having common internalizing cell surface receptors (such as transferrin); for example fibroblasts. If one was selecting on a tumor cell line (for example a breast tumor cell line), than one could negatively select on a normal breast cell line.

"Virtually any cell" would include live cells. Moreover, one of skill in the art appreciates that dead cells undergo rapid deterioration typically resulting the protein degradation . Such cells would be less likely to bear "all the markers on the target cell".

The specification thus clearly contemplates that subtractive cells include live cells and the rejection of claim 52 under 35 U.S.C. §112, first paragraph, should be withdrawn.

**Claims 55 and 56:**

The Examiner alleged the limitation "removing comprises contacting the target cells with trypsin" has no clear support in the specification as originally filed. Applicants traverse.

The specification, as amended,, at page 28, lines 9-11, recites:

> In a preferred embodiment, where the cells are adherent, **the cells are trypsinized** to free the cells from the extracellular matrix which may contain phage antibodies that bind the extracellular matrix. [emphasis added]

Similarly, at page 49, lines 8-10, the specification states:

> For some experiments, **cells were trypsinized after the three stripping buffer washes**, collected in a 15 ml Falcon tube, washed twice with PBS and then lysed with TEA. [emphasis added]

The specification also states, at page 54, lines 11-12:

> **To reduce the background of non-specific phage recovery, we studied the effect of trypsinizing the cells** prior to TEA lysis. [emphasis added]

There simply is no question that Applicants were in possession of a method that involved contacting the target cells with trypsin. Accordingly, the rejection of claims 55 and 56 under 35 U.S.C. §112, first paragraph, should be withdrawn.

**35 U.S.C. §112, Second Paragraph.**

Claims 1-17 and 51-57 were rejected under 35 U.S.C. §112, second paragraph, as described below.

**A) "Strong Wash"**

Claims 1 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite in the recitation of "a strong wash". Applicants traverse.

It is well recognized that the imprecise nature of the subject matter itself may limit the definiteness with which an invention may be described and that this should not prejudice the applicant. Thus a claim is deemed definite if "... read in light of the specification [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech Inc. v Monoclonal Antibodies, Inc.,* 231 USPQ 81 (Fed. Cir. 1986) *cert. denied* 480 U.S. 947 (1987) *citing Shatterproof Glass,* 225 USPQ 634, 641 (Fed. Cir. 1985).

In the instant case, the specification states:

> The "strong" washing step **is intended to remove tightly**- and weakly-bound surface phage. [emphasis added]

One of skill in the art would readily appreciate that a strong wash is a wash step capable of removing tightly bound surface phage. The use of a strong wash to remove tightly bound antibodies is well known to those of skill in the art. It is also well recognized that a strong wash can take a number of forms, *e.g.* low pH, a glycine wash, and the like.

The language "a strong wash" thus reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and is as precise as the subject matter permits. Accordingly, Applicants have met the requirements of 35 U.S.C. §112, second paragraph, and the rejection of claim 1 on these grounds should be withdrawn.

**B) Allegedly Critical Steps**

Claim 1 was also rejected under 35 U.S.C. §112, second paragraph, as indefinite, for allegedly failing to recite critical steps. In particular, the Examiner alleged that the claim is incomplete for failing to recite how the internalized member s of the library are identified. Applicants respectfully traverse.

The Examiner is respectfully reminded that "[a] patent need not teach, and preferably omits, what is well known in the art." See M.P.E.P. ' 2164.01 citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

In the instant case, methods of detecting phage internalized into cells are well known to those of skill in the art. Indeed, as stated in the specification:

> The internalized phage display library members can be identified directly or indirectly. Direct identification can be accomplished simply by visualizing the phage within a cell *e.g.* via immunofluorescent or confocal microscopy. Phage internalization can be identified by their ability to deliver a reporter gene that is expressed within the cell. The reporter gene can be one that produces a detectable signal (*e.g.* a fluorescent (*e.g.* lux, green fluorescent protein, *etc.*) or colorimetric signal (*e.g.* HRP, β-galactosidase) or can itself be a selectable marker (*e.g.* an antibiotic resistance gene). The use of both ∃-galactosidase and GFP as reporter genes in such phage is described herein.
>
> Alternatively, the phage display member can bear a marker (*e.g.* a label) and cells containing the internalized phage can be detected simply by detection of the label (*e.g.* in a flow cytometer). The direct methods preferably used for identification of the receptors or cells that are bound after selections are

> performed. It is noted that cell sorting approaches (FACs) will work with identification of either surface bound or internalized phage. However, an additional level of specificity can be achieved if the cells are first sorted for the presence of internalized phage prior to lysis. Direct methods are also used during the analysis phase to demonstrate that the phage selected are indeed internalized.
>
> Alternatively the internalized phage display library members can be identified indirectly. In indirect detection methods the phage-display library member(s) do not need to be detected while they are present within the cell. It is sufficient that they simply have been internalized.
>
> Indirect identification is accomplished for example, by isolating and expanding the phage that were internalized into the cells as described below. Indirect identification is particularly well suited where the identified phage display library members are going to be used in subsequent rounds of selection or to isolate bacteria harboring monoclonal phage genomes for subsequent monoclonal phage characterization (that is for the analysis of selection results).

Clearly, the numerous methods of identifying the internalized phage are contemplated by the present invention. Because such methods are well known to those of skill in the art, the need not be explicitly recited in the claim. Moreover, such recitation would unduly limit the claim and unfairly deny Applicants the scope to which that are rightfully entitled. Accordingly, the rejection of claim 1 under 35 U.S.C. §112, second paragraph, on these grounds should be withdrawn.

**C) Antecedent Basis.**

Claims 8, 10, 16, and 17 were rejected under 35 U.S.C. §112, second paragraph, as indefinite, for allegedly lacking antecedent basis for the language ""step (ii) is performed at a temperature lower than step (iv)" (claim 10), and for the language "said cells of a subtractive cell line" (claims 8, 16 and 17). The claims are amended herein to provide proper antecedent basis thereby obviating this rejection.

**35 U.S.C. §102(b).**

Claims 1-7, 12-15, and 53 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Barry *et al.* (1996) *Nature* Medicine, 2(3): 299-305).. Applicants traverse. Barry *et al.* fails to teach all of the elements of the presently claimed invention. Claim 1 recites:

> 1. (Currently Amended) A method of selecting a polypeptide that is internalized into a target cell, said method comprising:
>
> i) contacting one or more target cells with one or more members of a phage display library displaying one or more polypeptides;
>
> ii) washing said target cells **to remove and eliminate** members of said library that are bound to the exterior surface of said target cells, wherein said washing comprises washing said target cells with a strong wash;
>
> iii) culturing said target cells under conditions where members of said phage display library bound to an internalizing marker can be internalized; and
>
> iv) identifying internalized members of said phage display library that are internalized into one or more of said target cells, where said internalized members of said phage display library each display a polypeptide that is internalized into a target cell. [emphasis added]

Claim 1 indicates that the strong wash is used **to remove and eliminate phage** attached to the surface of the target cells. The removed phage are thus eliminated from further screening steps facilitating selection of internalizing phage.

In contrast, **Barry *et al* expressly teaches recovering the phage removed from the target cell surface and using those phage in subsequent panning rounds**:

> Binding was conducted at 4° C to avoid endocytosis of the phage. Ten library equivalents of the 12-amino acid polymer (12-mer) library ($3 \times 10^9$ phage from ON159.3) were incubated on the cells, the cells were washed, and **the acid-labile phage were eluted from the cell surface and recovered as the acid-eluted fraction**. In the first round of selection, approximately $10^{-6}$ of the input phage were eluted by acid (data not shown). Although peptide-presenting phage are usually recovered from their target molecule by using alow pH wash[4,5], slightly more phage remained associated with the cells following multiple acid washes than were eluted by the acid. **This cell associated fraction was also recovered and amplified because** these phage might have higher affinities for the cells or involve hydrophobic interactions. [emphasis added] (page 299, column 2)

This is further illustrated in Figure 1b which illustrates the recycling (rescreening) of the acid-eluted fraction of phage.

**Barry *et al.* thus fails to disclose a method in which the phage that bind the target cell surface are removed and eliminated** and therefore fails to anticipate the claimed invention.

Accordingly, the rejection of claim 1 and dependent claims 2-7, 12-15, and 53 under 35 U.S.C. §102(b) in light of Barry *et al.* should be withdrawn.

Claims 1-17 and 12-15 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Larocca *et al.* (U.S. Patent 6,054,312). Applicants traverse.

As indicated above, step ii of claim 1 expressly recites:

> ii) washing said target cells **to remove and eliminate** members of said library that are bound to the exterior surface of said target cells, wherein said washing comprises washing said target cells with a **strong wash**; [emphasis added]

Larocca *et al.* offers no disclosure or teaching of a method that involves using a **strong wash to** remove and eliminate members of a library that are bound to the surface of target cells. Should the Examiner wish to maintain this rejection, Applicants request that the Examiner identify with particularity (*e.g.* by column and line number) where Larocca *et al.* teaches such a wash step.

**35 U.S.C. §103(a).**

Claims 1-17 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Barry *et al.* (1996) *Nature Medicine* 2(3): 299-305, in view of either Ewijk *et al.* (1997) *Proc. Natl. Acad. Sci. U.S.A.*, 94:3903-3908 or Stausbol-Gron *et al.* (1996) *FEBS Letts*, 39: 71-75. Claims 1-17, 51-54, and 57 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Larocca *et al.* (U.S. patent 6,054,312 in view of either Ewijk *et al.* (1997) *Proc. Natl. Acad. Sci. U.S.A.*, or Stausbol-Gron *et al.* (1996) *FEBS Letts.* 39: 71-75. The Examiner alleges that Barry *et al.* and Larocca *et al.* teach the claimed method with the exception of the use of a subtractive cell line. The Examiner then alleged that Ewijk *et al.* teaches "the use of a subtractive approach using intact, mildly fixed thymic fragments as target tissue and thymocytes and spleen cells used to remove undesired specificities of the phage antibody library." (Office Action page 10, lines 18-20). The Examiner also alleged that Stausbol-Gron *et al.* teach the use of a subtractive panning strategy and that ". . . the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids." (Office Action, page 10, lines 10-12). Applicants traverse.

The Examiner is reminded that a *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the

elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger,* 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In the instant case, the combination of references cited by the Examiner fail to teach or suggest all of the elements of the presently claimed invention. Moreover, **combination of Stausbol-Gron *et al.* or Ewijk *et al.* with any of the primary references would result in a screening system unsuited to the detection of internalizing polypeptides**. Accordingly, the cited art offers no motivation to combine the references are proposed by the Examiner.

**A) The cited references fail to teach or suggest the presently claimed methods.**

The presently claimed invention provides a simple and efficient method of identifying of selecting a polypeptide that is internalized into a target cell. The method involves contacting the target cell(s) with a phage display library, using a **strong wash** to remove external phage that are tightly or weakly bound and identifying internalized members of the library. In certain embodiments, the target cells are contacted with **live cells** of a subtractive cell line.

**The cited art fails to teach or suggest the use of a strong wash to remove the undesired phage and identification/selection of the remaining internalized phage. The cited art also fails to teach or suggest the use of a subtractive cell line comprising cells, particularly living cells in combination with a strong wash.**

**i) Stausbol-Gron fails to teach a subtractive cell line or a strong wash.**

Contrary to the Examiner's assertion, Stausbol-Gron fails to teach a subtractive cell line or a strong wash. Stausbol-Gron teaches the use of a competitive two solid phage system for selecting phage. The system uses competitive proteins in solution or on the walls of an immunotube. There is no teaching or suggestion of a subtractive cell line comprising living cells.

Moreover, **Stausbol-Gron teaches wash conditions that utilize a weak wash** (phosphate buffered saline). Thus Stausbol-Gron expressly states:

> In the competitive two solid phase system, the target proteins, MIX + LDH proteins or FM55p **proteins were coated on immunobead(s)**. The second solid phase support was an **immunotube coated with competitive MIX proteins or competitive FM55p proteins, respectively**. Moreover, the **competitive proteins were added in solution**. [emphasis added] (Figure 1 legend).
>
> The immunobead was washed 20 times in **PBS with 0.2% Tween-20, and 20 times in PBS**. [emphasis added] page 72, column 1)

In addition, **Stausbol-Gron teaches the selection/use of the phage that are eluted off of the target (immunobeads), while the presently claimed methods contemplate selection/use of the phage that are retained (*i.e.*, internalized) by the target cells.** Thus, in contrast to the present invention Stausbol-Gron expressly teaches:

> The bound phage were eluted with 1 ml 100 M triethylamine for 10 min at room temperature and neutralized with 0.5 ml 1 M Tris, pH.7.4. Exponentially growing TG-1 bacteria **were infected with 1 ml of the eluate for 30 min at 37°C, and phage were produced by super-infection** with the helper phage VCS-M13 (Stragagene) and growing the bacteria with shaking overnight at 30°C. [emphasis added] (page 72, column 1)

Stausbol-Gron thus teaches the use of a "weak wash" (PBS), subtraction using isolated proteins in solution or attached to an immunotube, and selection of the phage washed off of the target. Stausbol-Gron fails to teach the use of a strong wash, of a subtractive cell line comprising living cells, or the selection of phage retained by the target immunobeads. The combination of Stausbol-Gron with Winter *et al.*, Barry *et al.*, or Larocca *et al.* simply fails to render the presently claimed invention obvious and the rejection under 35 U.S.C. §103(a) on these grounds should be withdrawn.

**ii) Stausbol-Gron teaches away from a strong wash.**

Stausbol-Gron actually teaches away from the use of a strong wash. In particular, this reference expressly states:

> The dilemma remains, however, that **attempts to improve the efficiency f selection inhibition by using higher stringency during the panning rounds will tend to decrease the diversity in the subtracted phage pool, because low affinity binders are lost [33]. Consequently, a less stringent**

> **approach may be more suitable** in some cases. [emphasis added] (page 74, column 2)

Stausbol-Gron thus expressly states that a strong wash (*i.e.*, high stringency) can [undesirably] decrease the diversity of the phage pool by eliminating low affinity binders and **teaches that lower stringency is desirable**. In contrast, the presently claimed methods pertain to the use of a strong wash (*e.g.* high stringency). Contrary to Stausbol-Gron, in the presently claimed methods it is desirable to eliminate strong binders that are not internalized into the target cells. Thus, the present specification expressly states:

> A second strong washing step is preferably used after internalization of members of the phage display library. **The "strong" washing step is intended to remove tightly- and weakly-bound surface phage.** [emphasis added] (specification, page 26, lines 25-28)

By teaching the desirability of a weak wash, Stausbol-Gron expressly teaches away from the presently claimed methods. Again, the combination of Stausbol-Gron with Barry *et al.*, or Larocca *et al.* simply fails to render the presently claimed invention obvious and the rejection under 35 U.S.C. §103(a) on these grounds should be withdrawn.

**iii) The defects of Stausbol-Gron are not remedied by Ewijk *et al.***

Ewijk *et al.* also fails to teach the use of a strong wash to eliminate the undesired/unselected phage. Rather, Ewijk *et al.* teaches the use of a "weak wash" for phage selection:

> The following day thymic fragments were allowed to sediment, the supernatant was decanted, and the thymic fragments were vigorously rinsed, using a total volume of 2 linters of M-PBS containing 0,05% Tween 20 (M-PB-Tw), **to remove nonspecifically adhered phages**. [emphasis added] (page 3904, column 1).

Ewijk *et al.* then utilizes use a strong wash (pH 2.5) **to elute and re-screen the desired phage rather than to remove and eliminate undesired phage**:

> To elute specifically bound phages, thymic fragments were transferred in a volume of 300 μl of M-PBS-Tw to a 15 –ml tube containing 450 μl of

> sodium citrate (**pH 2.5**). After 5 min, the pH was neutralized by adding 375 $\mu$l of 1 M Tris-HCl buffer (pH 7.4). Finally, 3 ml of 2TY medium (GIBCO/BRL) and 3 ml of Escherichia coli XL-1 blue (Stratagene) was added. Infection was allowed to proceed for 30 minutes. Bacteria were centrifuged at 2,2000 Xg for 30 min, suspended in 0.5 ml of 2TY, and plated on agar plates containing 25 $\mu$g/ml tetracycline, 100 $\mu$g/ml ampicillin, and 55 glucose (TAG) After overnight culture at 37°C, plates were scraped and bacteria were frozen in stock vials **or used to prepare the next library as describe in detail elsewhere(13)**. [emphasis added] (page 3904, column 1).

**Ewijk *et al.* thus discloses a method that is essentially the opposite of the presently claimed method**. Ewijk *et al.* teaches the use of a weak wash to screen for binding phage and the use of a strong wash to elute and recover the desired binders. In contrast, the presently claimed method contemplates the use of a strong wash to eliminate all externally bound phage including those that specifically bind to the target cells. The remaining **internalized** phage are then recovered. Ewijk *et al.* thus leads one of skill away from the presently claimed methods.

Ewijk *et al.* also fails to teach or suggest a subtraction with a subtractive cell line comprising **living cells**. To the contrary, Ewijk *et al.* expressly teaches the use of fixed (dead cells:

> To prepare stromal cells for phage selection, **we mildly fixed thymic tissue** with a solution of **0.05% gluteraldehyde** (Polysciences) in PBS using the total body perfusion fixation (16). [emphasis added] (page 3904, column 1)
>
> * * *
>
> To this solution, 1 ml of M-PBS, containing 2.5 x $10^8$ 005% **gluteraldehyde-fixed** adsorber cells (thymocytes + spleen cells), was added and allowed to incubate for 1 hr at room temperature. [emphasis added] (page 3904, column 1)

Ewijk *et al.* thus fails to teach the use of a strong wash to eliminate the undesired phage or to teach the use of a live cell line. Thus, Ewijk *et al.* taken with any or all of the primary references fails to teach or suggest the presently claimed invention. Accordingly, the rejection under 35 U.S.C. §103(a) on these grounds should be withdrawn.

**iv) Ewijk *et al.* teaches away from the presently claimed invention.**

Moreover, Ewijk *et al.* teaches away from the presently claimed invention. Ewijk *et al.* teaches a method for detecting **surface antigen**, not internalizing polypeptides. Thus Ewijk *et al.* expressly states:

> **Although our selection method was aimed to isolate MoPhabs directed to cell surface determinants expressed on intact thymic stromal cells**, several of the isolated MoPHabs recognized molecules expressed in the cytoplasm of stromal cells. This result may be inherent n the present procedure: after fixation, the thymus was cut into fragments thus exposing cytoplasmic determinants.

In addition, because Ewijk *et al.* teaches the use of fixed (dead) cells as target cells, the reference leads one of skill away from methods that can be used to detect internalizing polypeptides. Ewijk *et al.* thus leads one of skill away from the presently claimed invention consequently **fails** to support a *prima facie* case of obviousness.

**v. Barry *et al.* teaches away from the presently claimed invention.**

Barry *et al.* also teaches away from the present invention. Claim 1, as amended herein clarifies that the strong wash is used **to remove and eliminate phage** attached to the surface of the target cells. The removed phage are thus eliminated from further screening steps facilitating selection of internalizing phage.

As explained above, Barry *et al* expressly teaches recovering the phage removed from the target cell surface and using those phage in subsequent panning rounds:

> Binding was conducted at 4° C to avoid endocytosis of the phage. Ten library equivalents of the 12-amino acid polymer (12-mer) library ($3 \times 10^9$ phage from ON159.3) were incubated on the cells, the cells were washed, and **the acid-labile phage were eluted from the cell surface and recovered as the acid-eluted fraction**. In the first round of selection, approximately $10^{-6}$ of the input phage were eluted by acid (data not shown). Although peptide-presenting phage are usually recovered from their target molecule by using alow pH wash[4,5], slightly more phage remained associated with the cells following multiple acid washes than were eluted by the acid. **This cell associated fraction was also recovered and amplified because** these phage might have higher affinities for the cells or involve hydrophobic interactions. [emphasis added] (page 299, column 2)

This is further illustrated in Figure 1*b* which illustrates the recycling (rescreening) of the acid-eluted fraction of phage.

Barry *et al.* thus expressly leads one of skill away from a method in which the phage that bind the target cell surface are removed and eliminated and therefore leads one of skill away from the presently claimed invention. Accordingly, Barry *et al.* fails to support a *prima facie* case of obviousness and the rejection in light of Barry *et al* in view of either Ewijk *et al.* or Stausbol-Gron *et al.* should be withdrawn.

**B) The cited references offer no motivation to combine.**

The Examiner is also reminded that the MPEP expressly states that "if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP §2143.01, *citing In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

In the instant case, the combination of the methods of Stausbol-Gron or Ewijk *et al.* with the primary references (Barry *et al.*, and/or Larocca *et al.*) would produce systems unsatisfactory for the detection/selection of internalizing polypeptides and thus offer no motivation to make the modification(s) proposed by the Examiner.

**i) Stausbol-Gron teaches the use of cell-free extracts.**

Stausbol-Gron, *et al.* teaches the use of a two solid phase system comprising target protein(s) (antigen) attached to immunobeads and competitive proteins attached to an immunotube and in solution (*see* Figure 1, page 72). The reference offers no teaching or suggestion of the use of an intact cell. Use of the subtractive procedure taught by Stausbol-Gron *et al.* with the methods of Barry *et al.*, and/or Larocca *et al.*, would result in a cell-free screening system. **Lacking target cells, such a cell-free system cannot be used to identify internalizing antibodies.**

Modification of Barry *et al.*, and/or Larocca *et al.* with the subtractive methods disclosed by Stausbol-Gron *et al.* would render the art unsatisfactory for its intended purpose. Thus, as recognized in *In re Gordon,* and stated in MPEP §2143.01, there is no suggestion or motivation to make the proposed modification. Accordingly, the combination of Stausbol-Gron *et al.* with Barry *et al.*, and/or Larocca *et al.* does not support a *prima facie* case of obviousness and the rejection on these grounds should be withdrawn.

**ii) Ewijk *et al.* teaches the use of fixed (dead) cells.**

Ewijk *et al.* teaches the use of fixed (dead cells) as both "target cells" and to readsorb a library. The fixed target cells are dead and hence, incapable of internalizing a binding moiety. Modification of Barry *et al.,* and/or Larocca *et al.* with the methods disclosed by Ewijk *et al.* would produce a screening system using fixed cells that could not be used to screen for internalizing polypeptides. Accordingly, the combination of Ewijk *et al.* with Barry *et al.,* and/or Larocca *et al.* does not support a *prima facie* case of obviousness and the rejection on these grounds should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Tom Hunter
Reg. No: 38,498